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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/964,678	09/28/2001	Suzanne De La Monte	0609.4370002	3649

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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/964,678	Applicant(s) MONTE ET AL.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-9,14-16 and 35-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9,14-16,35-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Final Rejection

Claims 7-9, 14-16, 35-40 are pending examination.

Applicants' traversal, the amendment to claims 7, 14, 36, and the addition of claims 37-40 in paper no. 15 is acknowledged and considered.

Specification

The disclosure is objected to because of the following informalities: the status (e.g., pending, abandoned, patented US Patent No.) of US applications listed on pages 14 and 20-21 is missing.

Appropriate correction is required.

Claim Objections

Applicant's arguments, see paper no. 15, filed 1/22/03, with respect to the objection have been fully considered and are persuasive. The objection of claim 7 has been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 9, 14, 16, and 35-36 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 7, 9, 14, 16, and 35-36, as best understood, are readable on a genus of a DNA molecule of SEQ ID NO: 1 or a DNA molecule which is at least 90% homologous to SEQ ID NO: 1 wherein said DNA molecule is under control of a heterologous neuro-specific promoter, and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells, wherein the genus of DNA molecules is not claimed in a specific biochemical or molecule structure that could be envisioned by one skilled in the art at the time the invention was made.

The specification contemplates a genus of DNA molecules that code for a protein having the activity of SEQ ID NO: 1, which induces neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and/or irregular swollen neurites in a host which expresses the DNA sequence for use in producing a transgenic non-human animal (page 18, lines 28-30 and page 20, lines 1-2). The specification provides sufficient description of SEQ ID NO: 1 and a nucleotide sequence encoding the amino acid sequence set forth in SEQ ID NO: 2. The specification provides sufficient description for a DNA molecule that codes for an AD7c-NTP protein when over-expressed in isolated neuronal cells. The art of record teaches that there is a variation within the genus of the claimed DNA molecules. The art of record further teaches that one nucleotide change in a DNA molecule could result in the loss of its biological activity. The essential nucleotides required for an activity of AD7c-NTP are absent from the specification. The specification does not provide sufficient description of a genus of DNA molecules with 90% homology to SEQ ID NO: 1 that codes for a protein that has an activity of AD7c-NTP when

over-expressed in neuronal cells. It is not apparent that on the basis of the applicants' disclosure an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the claimed invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of DNA sequences that must exhibit the disclosed biological functions as contemplated by the specification.

It is not sufficient to support the present claimed invention directed to a genus of a DNA molecule of SEQ ID NO: 1 or a DNA molecule which is at least 90% homologous to SEQ ID NO: 1 wherein said DNA molecule is under control of a heterologous neuro-specific promoter, and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of DNA molecules which is at least 90% homologous thereof, that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of a DNA molecule,

which displays at least 90% homology to SEQ ID NO: 1 that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicant's arguments filed 1/22/03 have been fully considered but they are not persuasive. In view of the specification and the art of record at the time the application was filed, the specification does not satisfy the written description requirement to reasonably clarify to those skilled in the art, as of the effective filing date, applicants were in possession of the claimed invention.

The as-filed specification fails to provide the essential nucleotide or amino acid residues for a representative number of sequences, wherein each sequence is composed of at least 90% homologous to SEQ ID NO: 1, that has an activity of AD7c-NTP when expressed (under expression, normal expression, etc.) in neuronal cells, wherein said overexpression of said sequence results in the reduction of frequency of at least one of neuritic sprouting, nerve cell death, degenerating neurons, neurofibrillary tangles, or irregular swollen neurites and axons in said cells. The MPEP 2163 states:

> A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. For example, even though

a genetic code table would correlate a known amino acid sequence with a genus of coding nucleic acids, the same table cannot predict the native, naturally occurring nucleic acid sequence of a naturally occurring mRNA or its corresponding cDNA. Cf. In re Bell, 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993), and In re Deuel, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995) (holding that a process could not render the product of that process obvious under 35 U.S.C. 103). The Federal Circuit has pointed out that under United States law, a description that does not render a claimed invention obvious cannot sufficiently describe the invention for the purposes of the written description requirement of 35 U.S.C. 112. Eli Lilly, 119 F.3d at1567, 43 USPQ2d at 1405.

Thus, for the reasons set forth above, the as-filed specification does not provide sufficient description for a genus of nucleotide sequences with up to 140 different nucleotides (90% homology) to SEQ ID NO: 1 and possesses the biological activity of SEQ ID NO: 1 (AD7c-NTP) when over-expressed in neuronal cells.

Claims 7-9, 14-16, and 35-36 remain and claims 37-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification discusses that the invention features a genus of transgenic non-human animals, which over-expresses a DNA molecule set forth in SEQ ID NO: 1 or a DNA molecule which is at least 90% homologous thereto and goes on to contemplate that there are techniques available for producing transgenic animals (page 20). The specification requires that the starting material, which is a nucleic acid set forth in SEQ ID NO. 1 or a DNA molecule which is at least 90% homologous thereto, be used in a method of making a transgenic non-human animal comprising over-expressing SEQ ID NO: 1 or a sequence with 90% homology thereto. The specification contemplates that the transgenic animals can be used in a method for identifying compounds that could be potential useful for the treatment or prevention of Alzheimer's disease (AD) (page 21). In addition, the specification states that, "SEQ ID NO: 1 is observed in patients with (AD)".

As stated above, the specification requires the claimed DNA molecule for producing transgenic non-human animals. In view of In Re Wands Factors, the specification teaches one skilled in the are how to make a DNA molecule comprising the nucleotide sequence set forth in SEQ ID NO: 1 or comprising a nucleotide sequence encoding the amino acid sequence set forth in SEQ ID NO: 2. The specification does not provide sufficient guidance or factual evidence for one skilled in the art to practice the full scope of the claimed invention. The specification does not disclose which nucleotides of the claimed DNA molecule is considered essential for one skilled in the art to make a representative number of DNA molecules with 90% homology to SEQ ID NO: 1. In view of the art of record and the as-filed specification, it is apparent that one skilled in the art would be able to determine a DNA molecule with 90 percent homology to SEQ ID NO: 1. However, the specification does not provide sufficient guidance or factual evidence

for one skilled in the art to determine without an undue amount of experimentation to determine if the nucleic acid sequence with at least 90 percent homology to SEQ ID NO: 1, would exhibit the same biological function of SEQ ID NO: 1 (observed activity when the sequence is over-expressed in neuronal cells). Since, the relationship between a sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Ngo et al. The protein folding problem and tertiary structure prediction, 1994, Merz et al (ed.) Birkhauser, Boston, MA pp. 433 and 492-495 and Chiu et al., *Folding and Design*, 1998, pp. 223-228, cited on a prior 892), it would required undue experimentation for one skilled in the art to arrive at other DNA molecules with 90% homology to SEQ ID NO: 1 and having SEQ ID NO: 1 activity when over-expressed in neuronal cells. In addition, in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for the determination of other nucleotide sequences that are embraced by the claims. This is the case here. In other words, since it would require undue experimentation to identify other DNA sequences with at least 90% identity to SEQ ID NO: 1 and retaining the biological activity of SEQ ID NO: 1, it certainty would require undue experimentation to make their corresponding DNA and, therefore, one skilled in the art would not enabled to make a genus of DNA molecules with 90% homology to SEQ ID NO: 1. Therefore, the specification only provides sufficient guidance for making a DNA molecule comprising a nucleotide sequence

set forth in SEQ ID NO: 1 or a nucleotide sequence encoding the amino acid sequence set forth in SEQ ID NO: 2.

In addition, the as-filed specification does not provide sufficient guidance or factual evidence for using the DNA molecule for making a transgenic non-human animal expressing a nucleotide sequence encoding SEQ ID NO: 1 or a DNA molecule, which is at least 90% homologous thereto, and any corresponding phenotype.

It is further to note that the art of record at the time application was filed for producing transgenic animals with a predictable phenotype was considered unpredictable as exemplified by Polejaeva et al. Theriogenology, Vol. 53, pages 117-126, 2000, Polejaeva states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. See page 119.

In view of the concerns set forth by the art of record, the specification does not reasonably address the concerns put forth by the art of record encompassing any method for producing transgenic animals for use in over-expressing SEQ ID NO: 1 or a sequence with 90% homology to SEQ ID NO: 1 with a corresponding phenotype. In view of these factors and the concerns listed above, it is not apparent to one skilled in the art how to reasonably extrapolate from the specification to any transgenic non-human animal over-expressing SEQ ID NO: 1 or a nucleotide sequence with 90% homology thereto.

In addition, in view of the concerns stated above encompassing microinjection and random integration into a mammal's genome it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from random integration to determining if a DNA sequence set forth in SEQ ID NO: 1 is inserted at the correct site and is expressed at a level sufficient enough to produce a phenotype in any transgenic non-human animal. Furthermore, each non-human animal comprises a distinct genome and the specification does not provide sufficient guidance for how to avoid random integration of a DNA molecule set forth in SEQ ID NO: 1, which would result in the characteristics contemplated in the specification. In addition, Trojanowski teaches that certain characteristic can be produce in a test tube, the conditions required are highly artificial and in vitro paradigms have limited utility as models of in vivo mechanisms of neurodegeneration (Brain Pathology, Vol. 9, page 737, 1999). Thus, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from a human having AD that endogenously over-expresses AD7c-NTP to a transgenic non-human animal expressing AD7c-NTP with a desired phenotype because of the art of record and the distinct genomic structure of each non-human animal.

In addition, the specification fails to provide any relevant teachings or sufficient guidance with regards to the production of any transgenic non-human animals comprising a transgenic sequence encoding SEQ ID NO: 1 or a sequence with 90% homology thereto, which over-expresses the transgenic sequence such that a phenotype occurs. Furthermore, the as-filed specification fails to describe any particular phenotype exhibited by any contemplated transgenic non-human animal of the invention when the nucleotide sequence is over-expressed in said animal. Thus, as enablement requires the specification to teach how to make and/or use the

claimed invention, the specification fails to enable the production of any transgenic animal over-expressing SEQ ID NO: 1 or a sequence with 90% homology thereto.

[Note that although the claimed transgenic animal is not limited to expression of the protein at a level resulting in a specific phenotype, with regard to the claims breadth, the standard under 35 U.S.C. 112, first paragraph, entails the determination of what claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest interpretation of the claimed transgenic animal having cells, which harbor a recombinant nucleic acid that expresses the protein at a level sufficient to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic animal would serve if the transgene (e.g. SEQ ID NO: 1 or a sequence with 90% homology thereto) is not expressed at a sufficient level for a resulting phenotype).]

As the specification fails to provide any relevant teachings or sufficient guidance with regard to the production of a representative number of transgenic non-human animals as claimed, one skilled in the art would not be able to rely on the art of record for an attempt to produce any transgenic animals. This is because of the art of transgenic is not predictable art with respect to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic animal comprising a transgene of interest (e.g. SEQ ID NO: 1 or a sequence with 90% homology thereto); it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For example, the level and specificity of expression of a transgene (e.g. SEQ ID NO:

1 or a sequence with 90% homology thereto) as well as the resulting phenotype of the transgenic mammal are directly dependent on the specific transgene construct. The individual gene of interest, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of genetically modified animals, which exhibit a particular phenotype. This observation is supported by Wall (Theriogenology, 1996) who states "Our understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1997) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); e.g. specific promoters, presence or absence of introns, etc. The specification does not provide sufficient guidance, and it fails to feature any reasonable correlation between producing transgenic animal using microinjection of transgene into germ line and producing a transgenic animal which comprises a transgenic sequence encoding SEQ ID NO: 1 or a sequence with 90% homology thereto and which over-expresses the protein in the transgenic animal, and, thus, a specific resulting phenotype.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins states that "a given construct may react very differently from one species to another." See page S39, Summary. Wall et al. report "transgene expression and the

physiological consequences of transgene in animals are not always predicted in transgenic mouse studies." See page 62, first paragraph. Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, because, for example, the cis-acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 239-239). Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of a representative number of transgenic animal that over-expresses SEQ ID NO: 1 or a sequence with 90% homology thereto, it would require an undue amount of experimentation to reasonably predict the results achieved in any transgenic animal comprising a transgenic sequence set forth in SEQ ID NO: 1 or a sequence with 90% homology thereto and which over-expresses the protein in the transgenic animal at the levels of the claimed product, the consequences of that production, and therefore, the resulting phenotype.

Thus, in view of the In re Wands' Factors, the specification is not enabled for the claimed invention because in view of the undue quantity of experimentation necessary to determine the parameters listed above for the starting material, the lack of direction provided by the as-filed specification for the production of any transgenic non-human animal with a particular phenotype when a nucleotide with 90% homology to SEQ ID NO: 1 is over-expressed in said non-human animal. Furthermore, the lack of working examples for the demonstration or the reasonable correlation to the production of any transgenic non-human animal, in particular when the over-expression of the SEQ ID NO: 1 must occur at a level resulting in a corresponding phenotype, the unpredictable state of the art with respect to the transgene behavior in transgenic non-human

animals of any species, it would require an undue amount of experimentation for one skilled in the art to make and/or use the claimed invention.

Applicant's arguments filed 1/22/03 have been fully considered but they are not persuasive. The applicants' traversal is not found persuasive because in view of the In Re Wands Factors, the specification does not provide sufficient guidance or evidence to make and use a genus of transgenic non-human animal whose genome comprises a DNA molecule of SEQ ID NO: 1 or a DNA molecule, which is at least 90% homologous thereto. The as-filed specification does not provide sufficient guidance for a representative number of species of transgenic non-human animals comprising a nucleotide sequence that has an activity of AD7c-NTP when over-expressed in neuronal cells.

Furthermore, the as-filed specification lacks sufficient or factual evidence for which specific nucleotide sequence exhibits the function as contemplated by the breadth of the claims (same activity as AD7c-NTP when over-expressed in neuronal cells) since it is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the nucleotide sequence in many instances. The effects of these changes are largely unpredictable as to which mutation has a significant effect versus not (see Chiu and Ngo). It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement, e.g. Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997).

Furthermore, the as-filed specification does not provide sufficient guidance for making a transgenic non-human animal whose genome comprises a nucleotide sequence that has an

activity of AD7c-NTP when over-expressed in neuronal cells with a desired phenotype contemplated by the specification. Thus, in view of the art of record (e.g. Trojanowski) for extrapolating from in vitro results to an in vivo phenotype, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the lack of a working example for the claimed transgenic non-human animal and an *in vitro* culture comprising SEQ ID NO: 1 and its biological function when over-expressed to making transgenic animals whose genome comprise a DNA molecule of SEQ ID NO: 1 or a DNA molecule which is at least 90% homology thereto, and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells.

With respect to argument that the exhibits (B-E, filed on 8/8/02) showed production of transgenic mice with clinical and histologic similarities to a disease in humans, the argument is moot because the exhibits do not provide sufficient guidance or factual evidence for producing the claimed transgenic non-human animal. In addition, the exhibits do not use the same method and materials as contemplated by the specification.

Furthermore, with respect to the assertion that Trojanowski does not support that the claimed invention is not enabled, because Trojanowski reports the successful production of transgenic lines that over-expressed the tau protein and that exhibited "pre-tangle" tau pathology. The assertion is not found persuasive because Trojanowski teaches that, "transgenic lines that over-express the tau protein resulted in "pre-tangle" tau pathology, but no filamentous tau inclusions was observed. Thus, the desired phenotype (filamentous tau inclusion) was not observed in the transgenic mice, further supporting the unpredictability of over-expressing a protein in the brain of an animal and observing a desired phenotype.

Furthermore, it is acknowledged that there are several methods to produce transgenic non-human animals that are known in the art, however, the art of record provides concerns associated with predicting a desired phenotype in a transgenic non-human animal (e.g. Trojanowski, Rulicke, Mullins, Polejaeva). The rejection is directed to the unpredictability and the lack of working examples for the demonstration and/or the reasonable correlation to making and using any transgenic animal, in particular when the expression of the AD7c-NTP must occur at a level resulting in a corresponding phenotype. The specification teaches cloning AD7c-NTP into a Lac-Switch expression vector and stably transforming neuronal cells with said vector. The Lac-Switch expression vector does not contain a neuro-specific promoter and the specification does not teach how to use a neuro-specific promoter for production of the claimed transgenic animals. De La Monte states, "We were unable to investigate whether over-expression of AD7c-NTP might contribute to AD neurodegeneration using standard transfected cells because of the depletion of cell in culture (De La Monte et al., Journal of Neuropathology an Experimental Neurology, Vol. 60, pages 195-207, 2001)." In view of De La Monte, the specification does not provide sufficient guidance for one skilled in the art to over-express AD7c-NTP in cells of an animal and avoid depletion of cells resulting in death of the animal.

In addition, the art of record at the time the application was filed for producing a transgenic non-human animal model with a desired phenotype was considered unpredictable. The art of record (see De La Monte) is absent for making a transgenic non-human animal whose genome comprises AD7c-NTP and has a phenotype contemplated by the specification. The art of record displays the unpredictability of making an animal model using amyloid Beta protein, which is also over-expressed in the brain of patients with AD. Mucke et al., (Brain Research,

Vol. 666, 51-167, 1994); Sandhu, (Age, 17, 7-11, 1994); Malherbe et al., (Neurobiology of Aging, 17, 205-214, 1996); Loring et al., (Neurobiology of Aging, 17, 173-182, 1996) further support Trojanowski that in vitro observations do not correlate to a predicted phenotype in a transgenic animal model. In view of the art of record displaying the unpredictability of random integration of DNA into a cell's genome and transgene behavior, and the lack of guidance provided by the specification for making and using transgenic non-human animal having cells, which harbor a recombinant nucleic acid that expresses the protein at a level sufficient to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic animal would serve if the transgene (e.g. AD7c-NTP) is not expressed at a sufficient level for a resulting phenotype). Therefore, it is not apparent to one skilled in the art how a transgenic non-human animal can be used in an assay for screening a candidate drug of Alzheimer's disease, neuroectodermal tumors, malignant astrocyomas, and glioblastomas in a transgenic non-human animal comprising a nucleotide sequence that is SEQ ID NO: 1 or 90% homologous to SEQ ID NO: 1, if a phenotype comprising neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and/or irregular swollen neurites in neuronal cells is not observed in the transgenic animal. The claims are claiming subject matter that is not supported by the as-filed specification. Thus, in view of the In Re Wands Factors, it would take one skilled in the art an undue amount of experimentation for one skilled in the art to reasonably extrapolate from SEQ ID NO: 1 and its biological function when over-expressed in isolated neuronal cells to predicting the phenotype of a non-human animal whose genome comprises the claimed DNA molecule.

Furthermore, with respect to the assertion that the specification provides methods for making a genus of transgenic non-human animals comprising a stably integrated DNA molecule,

which is at least 90% homologous to SEQ ID NO: 1 that has AD7c-NTP activity when over-expressed in neuronal cells.

The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification

(See page 27 of traversal, which states, "transgenic animals of the present invention, even if they do not exhibit a particular phenotype, would nonetheless by useful for drug screening applications" provide no more than a plan or invitation in view of the art of record exemplifying the unpredictability of making and using a transgenic non-human animal comprising a nucleotide sequence of SEQ ID NO: 1 or a nucleotide sequence with 90% homology to SEQ ID NO: 1, wherein the nucleotide sequence encodes an amino acid sequence that has an activity of a AD7c-NTP protein when expressed in neuronal cells, for those skilled in the art to experiment with level of expression so as to provide any characteristic contemplated by the specification or any other characteristics not supported by the specification at the time the invention was made. See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor,

or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for what amino acids are required for a DNA molecule with 90% homology to SEQ ID NO: 1, wherein the DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells and using the claimed DNA molecule for producing a transgenic non-human animal with a desired phenotype or a phenotype not supported by the as-filed specification, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the assertion in the specification to the claimed invention. Therefore, the as-filed specification is not enabled for the claimed invention.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

Brian Whiteman
Patent Examiner, Group 1635

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER